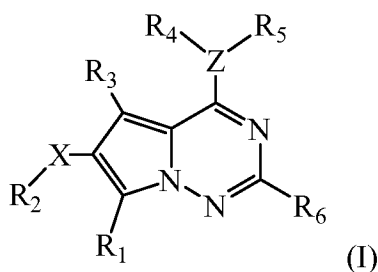


AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) A method of treating one or more conditions associated with p38 kinase activity wherein said conditions are selected from asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, ~~diabetes~~, inflammatory bowel disease, osteoporosis, ~~psoriasis~~, graft vs. host rejection, ~~atherosclerosis, and arthritis including rheumatoid arthritis~~, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis and osteoarthritis, comprising administering to a patient in need thereof at least one compound having the formula (I):



or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

R₃ is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH₂;

X is selected from -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, -NR₁₀-, -NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-, -NR₁₀SO₂NR₁₁-, -SO₂NR₁₀-, -C(=O)NR₁₀-, halogen, nitro, and cyano, or X is absent;

Z is selected from O, S, N, and CR₂₀, wherein when Z is CR₂₀, said carbon atom may form an optionally-substituted bicyclic aryl or heteroaryl with R₄ and R₅;

R₁ is hydrogen, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂, -SO₂R₂₂, -SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₄R₂₅, -NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -NR₂₁C(=O)NR₂₄R₂₅, halogen, nitro, or cyano;

R₂ is selected from:

- a) hydrogen, provided that R₂ is not hydrogen when X is -S(=O)-, -SO₂-, -NR₁₀CO₂-, or -NR₁₀SO₂-;

- b) alkyl, alkenyl, and alkynyl optionally substituted with up to four R₂₆ or pentafluoroalkyl;
 - c) aryl and heteroaryl optionally substituted with up to three R₂₇; and
 - d) heterocyclo and cycloalkyl optionally substituted with keto (=O), up to three R₂₇, and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or
 - e) R₂ is absent if X is halogen, nitro or cyano;
- (i) R₄ is substituted aryl, aryl substituted with NHSO₂alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring, and
R₅ is hydrogen, alkyl, or substituted alkyl, except when Z is O or S, R₅ is absent,
or alternatively,
- (ii) R₄ and R₅ taken together with Z form an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl;
- R₆ is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, -NR₇R₈, -OR₇, or halogen;
- R₁₀ and R₁₁ are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and substituted heterocyclo;
- R₇, R₈, R₂₁, R₂₄, and R₂₅ are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, ~~heterocycle~~ heterocyclo, and substituted heterocyclo;
- R₂₀ is hydrogen, lower alkyl, or substituted alkyl, or R₂₀ may be absent if the carbon atom to which it is attached together with R₄ and R₅ is part of an unsaturated bicyclic aryl or heteroaryl;
- R₂₂ is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;
- R₂₆ is selected from halogen, trifluoromethyl, haloalkoxy, keto (=O), nitro, cyano, -SR₂₈, -OR₂₈, -NR₂₈R₂₉, -NR₂₈SO₂, -NR₂₈SO₂R₂₉, -SO₂R₂₈, -SO₂NR₂₈R₂₉, -CO₂R₂₈, -C(=O)R₂₈, -C(=O)NR₂₈R₂₉, -OC(=O)R₂₈, -OC(=O)NR₂₈R₂₉, -NR₂₈C(=O)R₂₉, -NR₂₈CO₂R₂₉, =N-OH, =N-O-alkyl; aryl optionally substituted with one to three R₂₇; cycloalkyl optionally substituted with keto(=O), one to three R₂₇, or having a carbon-carbon bridge of 3 to 4 carbon atoms; and heterocyclo optionally substituted with keto (=O), one to three R₂₇, or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R₂₈ and R₂₉ are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C₃₋₇cycloalkyl, and C₃₋₇heterocycle, or

may be taken together to form a C₃₋₇heterocycle; and wherein each R₂₈ and R₂₉ in turn is optionally substituted with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy; and R₂₇ is selected from alkyl, R₃₂, and C₁₋₄alkyl substituted with one to three R₃₂, wherein each R₃₂ group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, -SR₃₀, -OR₃₀, -NR₃₀R₃₁, -NR₃₀SO₂, -NR₃₀SO₂R₃₁, -SO₂R₃₀, -SO₂NR₃₀R₃₁, -CO₂R₃₀, -C(=O)R₃₀, -C(=O)NR₃₀R₃₁, -OC(=O)R₃₀, -OC(=O)NR₃₀R₃₁, -NR₃₀C(=O)R₃₁, -NR₃₀CO₂R₃₁, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R₃₀ and R₃₁ are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C₃₋₇cycloalkyl, and heterocycle, or may be taken together to form a C₃₋₇heterocycle.

2. (Previously Presented) The method of claim 1 comprising administering to the patient at least one compound having the formula (I), or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₃ is methyl, -CF₃, or -OCH₃;

X is selected from -C(=O)-, -NR₁₀-, -NR₁₀C(=O)-, -NR₁₀CO₂-, -NR₁₀SO₂-, -SO₂NR₁₀-, and -C(=O)NR₁₀-, or X is absent;

Z is N;

R₂ is hydrogen, C₂₋₆alkyl, C₁₋₄alkyl substituted with up to four R₂₆, pentafluoroalkyl, or aryl or heteroaryl optionally substituted with up to two R₂₇;

R₄ is phenyl substituted with one R₁₂ and zero to three R₁₃;

R₅ and R₁₀ independently are selected from hydrogen and lower alkyl;

R₁₂ is carbamyl, arylsulfonylamine, or ureido, each of which is optionally substituted with up to two of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or alkylsulfonylamine;

R₁₃ at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, -OR₁₄, -C(=O)alkyl, -OC(=O)alkyl, -NR₁₅R₁₆, -SR₁₅, -NO₂, -CN, -CO₂R₁₅, -CONH₂, -SO₃H, -S(=O)alkyl, -S(=O)aryl, -NHSO₂-aryl-R₁₇, -NHSO₂-alkyl, -CONHR₁₇, and -NHC(=O)NHR₁₇;

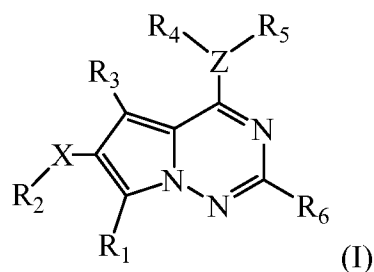
R₁₄ is hydrogen, alkyl, or aryl;

R₁₅ is hydrogen or alkyl;

R₁₆ is hydrogen, alkyl, aralkyl, or alkanoyl; and

R₁₇ is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl.

3. (Currently Amended) A method of treating one or more conditions associated with p38 kinase activity wherein said conditions are selected from asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, ~~diabetes~~, inflammatory bowel disease, osteoporosis, psoriasis, graft vs. host rejection, ~~atherosclerosis, and arthritis including rheumatoid arthritis~~, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis and osteoarthritis, comprising administering to a patient in need thereof at least one compound having the formula (I):



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₃ is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH₂;

X is selected from -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, -NR₁₀-, -NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-, -NR₁₀SO₂NR₁₁-, -SO₂NR₁₀-, -C(=O)NR₁₀-, halogen, nitro, and cyano, or X is absent;

Z is O, S, N, or CR₂₀;

R₁ is hydrogen, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂, -SO₂R₂₂, -SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -NR₂₁C(=O)NR₂₄R₂₅, halogen, nitro, or cyano;

R₂ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, aralkyl, substituted aralkyl, or heterocycloalkyl, or substituted heterocycloalkyl, or when X is halo, nitro or cyano, R₂ is

absent, provided that R_2 is not hydrogen when X is $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, or $-NR_{10}SO_2-$;

R_4 is substituted aryl, aryl substituted with $NHSO_2$ alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring system;

R_5 is hydrogen, alkyl, or substituted alkyl, except that when Z is O or S, R_5 is absent;

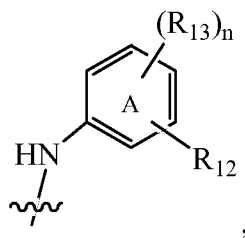
R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-NR_7R_8$, $-OR_7$, or halogen;

R_7 , R_8 , R_{10} , R_{11} , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

R_{20} is hydrogen, lower alkyl, or substituted alkyl; and

R_{22} is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo.

4. (Previously Presented) The method of claim 3 comprising administering to the patient at least one compound of formula (I), in which R_4 , R_5 and Z are represented by:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_{12} is attached to any available carbon atom of phenyl ring A and is selected from carbamyl, arylsulfonylamine, and ureido, each of which is optionally substituted with up to one of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or C_{1-4} alkylsulfonylamine;

R_{13} is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-OR_{14}$, $-C(=O)$ alkyl, $-OC(=O)$ alkyl, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$ alkyl, $-S(=O)$ aryl, $-NHSO_2$ -aryl- R_{17} , $-NHSO_2C_{1-4}$ alkyl, $-CONHR_{17}$, and $-NHC(=O)NHR_{17}$;

R_{14} is hydrogen, alkyl, or aryl;

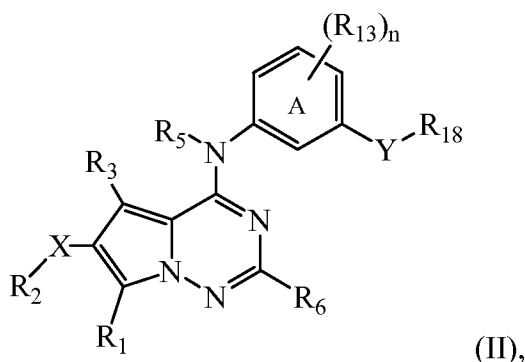
R₁₅ is hydrogen or alkyl;

R₁₆ is hydrogen, alkyl, aralkyl, or alkanoyl; and

R₁₇ is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl; and

n is 0, 1, 2 or 3.

5. (Previously Presented) The method of claim 3 comprising administering to the patient at least one compound having the formula (II):



or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

R₃ is methyl or CF₃;

X is $-\text{C}(=\text{O})\text{NR}_{10}-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, or $-\text{C}(=\text{O})-$;

R₁ is hydrogen, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, halogen, nitro, or cyano;

Y is $-\text{C}(=\text{O})\text{NH}-$, $-\text{NHC}(=\text{O})\text{NH}-$, or $-\text{NHSO}_2-$;

R₁₀ is hydrogen or lower alkyl;

R₁₈ is selected from hydrogen, alkyl, alkoxy, aryl, and aryl substituted with one to three R₁₉, except that when Y is $-\text{NHSO}_2-$, R₁₈ is C₁₋₄alkyl, aryl or aryl substituted with R₁₉;

R₁₃ is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-\text{OR}_{14}$, $-\text{C}(=\text{O})\text{alkyl}$, $-\text{OC}(=\text{O})\text{alkyl}$, $-\text{NR}_{15}\text{R}_{16}$, $-\text{SR}_{15}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{R}_{15}$, $-\text{CONH}_2$, $-\text{SO}_3\text{H}$, $-\text{S}(=\text{O})\text{alkyl}$, $-\text{S}(=\text{O})\text{aryl}$, $-\text{NHSO}_2\text{-aryl-R}_{17}$, $-\text{NHSO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{CONHR}_{17}$, and $-\text{NHC}(=\text{O})\text{NHR}_{17}$;

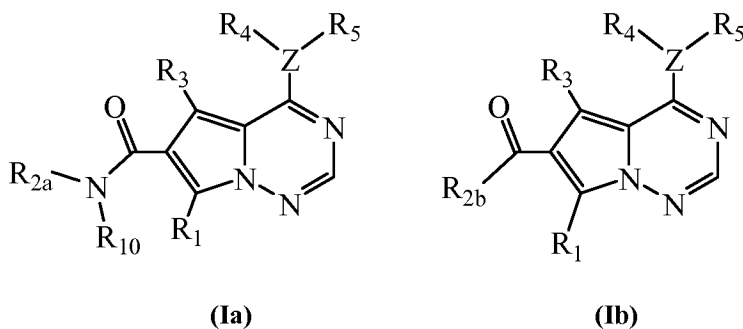
R₁₄, R₁₅, R₁₆ and R₁₇ are hydrogen or alkyl;

R₁₉ at each occurrence is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl,

carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, wherein each group R_{19} may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl; and

n is 0, 1 or 2.

6. (Previously Presented) The method of claim 3, comprising administering to the patient at least one compound having the formula (Ia) or (Ib):



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_3 is methyl or CF_3 ;

R_{2a} and R_{2c} are independently selected from hydrogen, C_{2-6} alkyl, substituted C_{1-4} alkyl, aryl, substituted aryl, benzyl, and substituted benzyl;

R_{2b} is heterocyclo or substituted heterocycle; and

R_{10} is hydrogen or lower alkyl.

7-8. (Cancelled).

9-11. (Cancelled).